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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/825,580 | 04/02/2001 | Michael J. Eppihimer | 08702.0006-00000 | 9952 |

22852 7590 09/09/2004

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
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| EXAMINER | |
|---|---|
| GAMBEL, PHILLIP | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/825,580 | EPPIHIMER ET AL. | |
| | Examiner | Art Unit | |
| | Phillip Gambel | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *6/25/04; 8/13/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20 and 25-57* is/are pending in the application.

4a) Of the above claim(s) *29,30,43,44 and 46-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,25-28,31-42,45 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.
Applicant's submission filed on 6/25/04 has been entered.

2. Applicant's amendment, filed 6/25/04, has been entered.
Claims 1, 2, 20, 25 and 26 have been amended.
Claims 21-24 have been canceled.
Claims 27-57 have been added.

Claims 1-20 and 25-57 are pending.

3. Upon consideration of applicant's amendment, filed 6/25/04, this application contains claims directed to the following patentably distinct species of the claimed Invention: wherein the disorder, condition or procedure of the subject targeted for treating or inhibiting thrombosis is selected from the group chosen from the disorders, conditions or procedures recited in claim 1 (a), (b) and (c).

These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic, for example.

4. Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

5. During a telephone conversation with Mary Ferguson on 8/13/04, a provisional election was made to prosecute the species of "hypertension"
Affirmation of this election must be made by applicant in responding to this Office Action.

Claims 29, 30, 43, 44, 46-49 have been withdrawn from consideration as being drawn to the non-elected species.

Claims 1-20, 25-28, 31-42, 45 and 50-57 are under consideration as they read on the elected species, hypertension.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-20, 25-28, 31-42, 45 and 50-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PSGL-1 and fragments thereof which "inhibit interaction P-selectin or E-selectin and a P-selectin ligand protein by inhibiting the interaction of P-selectin or E-selectin expressing endothelial cells and activated platelet with PSGL expressing leukocytes" (e.g. see page 5, paragraph 2 of the instant specification), including the P-selectin binding domains and fragments, does not reasonably provide enablement for any "PSGL-1 protein or a fragment thereof", including any "PSGL-1 or a fragment thereof having a P-selectin ligand activity"
The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient guidance and direction as to those inhibitory "PSGL-1 proteins or fragments thereof" that can treat or inhibit thrombosis other than those PSGL-1 and fragments thereof which "inhibit interaction P-selectin or E-selectin and a P-selectin ligand protein by inhibiting the interaction of P-selectin or E-selectin expressing endothelial cells and activated platelet with PSGL expressing leukocytes" (e.g., see page 5, paragraph 2 of the instant specification).

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. inhibit thrombosis) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of "PSGL-1 proteins and fragments thereof" and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant application, it is noted that various mutations, substitutions and the like provide a range of activities, no all which are necessarily predictive of "PSGL-1 proteins and fragments thereof" that can inhibit thrombosis". It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences as essential for in vivo characterization of their therapeutic potential to treat thrombosis, including hypertensions. A person of skill in the art could not predict which particular amino acid sequences or fragments of "PSGL-1" are essential to "PSGL-1 and fragments thereof" and could be used in the claimed therapeutic methods.

Because of the lack of sufficient guidance and predictability in determining which modifications would lead to "PSGL-1 protein and fragments thereof to inhibit thrombosis" and that the relationship between the sequence of a protein / peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of other functional PSGL-1 protein or fragments thereof to inhibit or treat thrombosis, including hypertension".

The recitation of "having a P-selectin ligand activity" does not require that the claimed "SGL-1 protein and fragments" thereof have the necessary inhibitory properties necessary to carry the claimed inhibition of thrombosis encompassed by the claimed methods.

Without sufficient guidance, the changes which can be made in the structure of "PSGL-1 proteins or fragments thereof to inhibit thrombosis" is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant is invited to the limit the claimed antagonists to "PSGL-1" and the "P-selectin ligand activity" of "PSGL-1 fragments to "PSGL-1" and "PSGL-1 fragments" with those activities (e.g. "binding or inhibiting") disclosed in the specification as filed and to those activities which can be readily measured.

Applicant is reminded to provide sufficient written support for any amended "limitations" to avoid new matter issues. See MPEP 714.02 and 2163.06

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-4, 8-13, 16-18, 25-28, 45-47, 50-53 and 57 are rejected under 35 U.S.C. § 102(e) as being anticipated by Cummings et al. (U.S. patent No. 5,464,778) (see entire document).

Cummings et al. teach the use of PSGL in the treatment of acute and chronic conditions associated with leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury, ARDS, atherosclerosis and myocardial ischemia, strokes, circulatory shock (see column 18, paragraphs 5-8; columns 19-20). Cummings et al. teach the properties and the use of PSGL (column 9-18), including protein fragments thereof (e.g. column 20, paragraph 3) as well as the administration and monitoring according to one of ordinary skill in the art (column 21, paragraphs 2-3). Although the reference is silent about "hypertension" per se, applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in the reference would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by Cummings et al. Further, the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is $LTC_4$) would have been inherent properties of the referenced methods of treating various acute and chronic conditions associated with thrombosis with PSGL and fragments thereof and the properties of said PSGL and fragments thereof at the time the invention was made.

Given the referenced treating of various acute and chronic conditions associated with thrombotic complications, it would have been inherent that such patients would have been identified as being subjects at risk of thrombosis. Cummings et al. also teach dosage ranges (e.g. 0.2 to 30 mg/kg body weight) for the treatment of inflammatory disorders (column 21, paragraph 1). Although this paragraph discloses carbohydrate inhibitors, the ordinary artisan would have immediately envisaged that this broad dosage range would have included other inhibitors (e.g. column 18, paragraph 4) as dictated by the specific condition (column 21, paragraphs 2-3). Also, given the nature of the acute and particularly the nature of chronic thrombotic conditions, one of ordinary skill at the time the invention was made would have provide the PSGL prior to thrombus formation.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999); Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). See MPEP 2112-2112.02.

10. Claims 1-5, 7-18, 25-28, 45—47 and 50-57 are rejected under 35 U.S.C. § 102(e) as being anticipated by Larsen et al. (U.S. Patent No. 5,840,679) (see entire document).

Larsen et al. teach the use of PSGL (e.g. ; columns 7-8, columns 13-18 and Examples), including fragments (e.g. columns 9-10) and fragments fused to carrier molecules such as immunoglobulins (e.g. chimeric forms of said PSGL (column 9-10, overlapping paragraph) to treat conditions characterized by P-selectin mediated intercellular adhesion, such as myocardial infarction and ARDS as well as hemodialysis and leukophoresis patients (columns 15-16, overlapping paragraph), including its combination with other pharmaceutical compositions, including anti-inflammatory and thrombolytic or anti-thrombotic agents (e.g. columns 16-18) (see entire document, including Summary of the Invention; Detailed Description of the Invention). The persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in the reference would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by Larsen et al. Larsen et al. also teach various modes of administration and dosing (e.g. liposomes, pharmaceutical carriers), including combinations of agents would be provided in therapeutically effective amounts either serially or simultaneously sufficient for the needs of the patient, including the nature and severity of the condition being treated according to the attending physician as well as doses ranges from about 0.1 ug to about 100 mg of isolated PSGL per kg body weight (columns 16-18). Larsen et al. teach soluble forms and fragments thereof which binds P-selectin comprising the same or nearly the same regions encompassed by the claimed human PSGL sequences (e.g. columns 9-15).

Given the referenced treating of various acute and chronic conditions associated with thrombotic complications, it would have been inherent that such patients would have been identified as being subjects at risk of thrombosis. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is $LTC_4$) would have been inherent properties of the referenced methods of treating various conditions associated with thrombosis with PSGL and fragments thereof and the properties of said PSGL and fragments thereof at the time the invention was made

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999); Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). See MPEP 2112-2112.02.

11. Claims 1-20, 25-28, 31-42, 45 and 50-57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. patent No. 5,464,778) AND Larsen et al. (U.S. Patent No. 5,840,679) in further view of Blann et al. (Journal of Human Hypertension 11: 607-609, 1997), Araneo et al. (U.S. Patent No. 6,150,348) and DeFrees et al. (U.S. Patent No. 5,604,207).

Cummings et al. teach the use of PSGL in the treatment of leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury and atherosclerosis (see column 18, paragraphs 5-8; columns 19-20, overlapping paragraph). Cummings et al. teach the properties and the use of PSGL (column 9-18), including protein fragments thereof (e.g. column 20, paragraph 3) as well as the administration and monitoring according to one of ordinary skill in the art (column 21, paragraphs 2-3). The claimed functional limitations would be expected properties of the referenced methods of treating atherosclerosis with PSGL and fragments thereof.

Cummings et al. differs from the claimed PSGL by not disclosing particular human PSGL sequences and domain structure thereof. Larsen et al. teach the structure, including the domain structure and the use of PSGL-derived fragments which are the same or nearly the same as that claimed (see columns 9-15).

Larsen et al. teach the use of PSGL (e.g. ; columns 7-8, columns 13-18 and Examples), including fragments (e.g. columns 9-10) and fragments fused to carrier molecules such as immunoglobulins (e.g. chimeric forms of said PSGL (column 9-10, overlapping paragraph) to treat conditions characterized by P- or E-selectin mediated intercellular adhesion, such as myocardial infarction (columns 15-16, overlapping paragraph), including its combination with other pharmaceutical compositions, including anti-inflammatory and thrombolytic or anti-thrombotic agents (e.g. columns 16-18) (see entire document, including Summary of the Invention; Detailed Description of the Invention).

Although Cummings et al. and Larsen et al. do not disclose all of the effective amounts recited in the instant claims 18-20, Cummings et al. and Larsen et al. teach the art known provision effective amounts of PSGL which inhibit P-selectin binding to treat thrombotic conditions to meet the severity of the condition and the needs of the patients. Therefore, the modes of administration and dosages encompassed by the claimed invention (claims 17-20) would have been met by the ordinary artisan at the time the invention was made to meet the severity of the conditions and the needs of the patients. For example, Larsen et al. also teach various modes of administration and dosing (e.g. pharmaceutical carriers), including combinations of agents would be provided in therapeutically effective amounts either serially or simultaneously sufficient for the needs of the patient, including the nature and severity of the condition being treated according to the attending physician (columns 16-18). ). Given the referenced treating of various acute and chronic conditions associated with thrombotic complications, it would have been inherent that such patients would have been identified as being subjects at risk of thrombosis.

Although Cummings et al. and Larsen et al. do not disclose the role of $LTC_4$ in thrombus formation and thrombotic conditions per se, $LTC_4$ was a known thrombus-inducing agent in thrombus formation and thrombotic conditions. Therefore, one of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by Cummings et al. and Larsen et al. would have inhibited the thrombus inducing agent in a subject, including $LTC_4$ at the time the invention was made.

The persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in the reference would have been intrinsically inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by Larsen et al. Although Cummings et al. and Larsen et al. do not disclose inhibiting hypertension and deep vein thrombosis by inhibiting P-selectin-PSGL-1 interactions per se, Blann et al., Araeneo et al. and DeFrees et al. all teach the role of such interactions in various thrombotic conditions, including hypertension and deep vein thrombosis at the time the invention was made.

Blann et al. teach that it was known that increased plasma levels of platelet specific products such as soluble P-selectin have been taken to imply increased platelet activation and that reversible platelet activation is present in hypertension (see entire document, including the Introduction). Blann et al. conclude that such changes associated with platelet activation may be partly responsible for the increases risk of thrombotic stroke and indicates that therapeutic strategies aimed at rescuing platelet activity may be beneficial (page 608, column 2, last paragraph).

Araneo et al. teach methods of preventing or reducing reperfusion injuries as well as ARDS, including preventing or reducing pulmonary hypertension via inhibiting the expression of P-selectin on endothelium (see entire document, including Summary of the Invention on columns 10-11 and Detailed Description of the Invention, including columns 11, 17 and Examples).

DeFrees et al. teach inhibitors of P-selectin-ligand interactions are especially useful in minimizing tissue damage that accompanies thrombotic disorders, including having therapeutic value in treating patients with stoke, myocardial infarctions, deep vein thrombosis and pulmonary embolism (see entire document, including column 45, paragraph 2).

One of ordinary skill in the art at the time the invention was made would have been motivated to administer PSGL-1, fragments and chimeric constructs thereof, provided they had the properties of inhibiting P-selectin or PSGL-1-mediated interactions and inflammatory responses, as taught by Cummings et al. and Larsen et al. to treat patients with various thrombotic conditions. Given the teachings of Cummings et al. and Larsen et al. to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary/thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit thrombosis, to increase the movement of cells relative to blood vessels and to inhibit the effect of thrombus-inducing agents, as properties of such treatment of PSGL-1-mediated interactions and inflammatory responses.

Given the role and indication of P-selectin in platelet activation and various thombotic disorders and the clear teaching of the prior art to target such platelet activation via P-selectin, such targeted conditions and disorders would have included hypertension, including pulmonary hypertension associated with ARDS as well as deep vein thrombosis, as taught by Blann et al., Araneo et al. and DeFrees et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claim 27 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Claims 1-20, 25-28, 31-42, 45 and 50-57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. patent No. 5,464,778) AND Larsen et al. (U.S. Patent No. 5,840,679) in further view of Blann et al. (Journal of Human Hypertension 11: 607-609, 1997), Araneo et al. (U.S. Patent No. 6,150,348) and DeFrees et al. (U.S. Patent No. 5,604,207)
as applied to claims 1-20, 25-28, 31-42, 45 and 50-57 above and in further evidence of Maugeri et al. (Thrombosis and Haemostasis 72: 450-456, 1994) and Johnston et al. (J. Immunol. 159: 4514-4523, 1997).

The teachings of Cummings et al. and Larsen et al. ) in further view of Blann et al. (Journal of Human Hypertension 11: 607-609, 1997), Araneo et al. (U.S. Patent No. 6,150,348) and DeFrees et al. (U.S. Patent No. 5,604,207) are set forth above.

Cummings et al. and Larsen et al. differ from the claimed methods by the claimed methods by not disclosing the role of $LTC_4$ in thrombus formation and thrombotic conditions per se, $LTC_4$ was a known thrombus-inducing agent in thrombus formation and thrombotic conditions as taught by Maugeri et al. and

Maugeri et al. teach that is was known at the time the invention was made that $LTC_4$ was one of the biologically active substances that play a role in inflammation and thrombosis (see entire document). Further, Maugeri et al. teach that anti-P-selectin antibodies can inhibit $LTC_4$ production (see Abstract, Results and Discussion). Further, Marugeri et al. discuss that neutrophil-platelet interaction via P-selectin plays a role in $LTC_4$ cooperative synthesis, which play a significant role in sever pathophysiological situations including inflammatory and cardiovascular diseases (see Abstract, Results and Discussion).

Johnston et al. teach that anti-P-selectin antibodies can inhibit inflammatory conditions, including $LTC_4$ induced leukocyte rolling in vivo (see entire document, including Abstract, Results and Discussion).

Again, although Cummings et al. and Larsen et al. do not disclose the role of $LTC_4$ in thrombus formation and thrombotic conditions per se, $LTC_4$ was a known thrombus-inducing agent in thrombus formation and thrombotic conditions, as evidenced by Maugeri et al. and Johnston et al.. Therefore, one of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by Cummings et al. and Larsen et al. would have inhibited the thrombus inducing agent in a subject, including $LTC_4$ at the time the invention was made. Further, both Maugeri et al. And Johnston et al. teach that inhibiting P-selectin-mediated events results in the inhibition of thrombus-inducing biological substances, including $LTC_4$.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer PSGL-1, fragments and chimeric constructs thereof, provided they had the properties of inhibiting PSGL-1-mediated interactions and inflammatory responses, as taught by Cummings et al. and Larsen et al. to treat patients with various thrombotic conditions. Given the teachings of Cummings et al. . and Larsen et al. to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary/thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit and to inhibit the effect of thrombus-inducing agents, as properties of such treatment of PSGL-1-mediated interactions and inflammatory responses. Given the role and indication of P-selectin in platelet activation and various thombotic disorders and the clear teaching of the prior art to target such platelet activation via P-selectin, such targeted conditions and disorders would have included hypertension, including pulmonary hypertension associated with ARDS as well as deep vein thrombosis, as taught by Blann et al., Araneo et al. and DeFrees et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
September 7, 2004